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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,464	02/11/2002	James Tiedje	MSU-06787	4392

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EXAMINER	
BAUSCH, SARAE L	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
04/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/073,464	TIEDJE ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14 and 22-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-14 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/04/2009 has been entered.

2. Currently, claims 1-6, 8-14, 22-28 are pending in the instant application. Claim 7 and 15-21 have been canceled.

Withdrawn Rejections

3. The rejection of claims 1-6, 8-14, and 22-27, under 35 USC 112, 1st paragraph made in section 5 of the previous office action mailed 09/09/08 is withdrawn in view of the amendment to the claims.

New Grounds of Rejection, Necessitated by Amendment to the claims

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 22 and 24 with the recitation of "between 60 and 500,000 of said genomic sequences" is not supported in the specification and raises the issue of new matter. The specification teaches 60 to 96 genome fragments were spotted on microarrays (see page 7, lines 5-6). The specification teaches that arrays containing up to approximately 100,000 DNA spots are used (see page 7, lines 20-22) and 500,000 probes (see pg. 11 lines 13-15), however the specification does not teach a range of up to 500,000 probes. Thus a range to encompass 60 and 500,000 is new matter as the specification does not teach nor contemplate a range of 60 to 500,000 genomic sequences are arrayed. The specification provides no indication of the criticality of the amended range. The specification does not provide support for the range of 60 to 500,000.

As discussed in MPEP 2163.05, section III, with respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d1481, 1487 (Fed. Cir. 2000) ("[T]he specification does not clearly disclose to the skilled artisan that the inventors... considered the... ratio to be part of their invention.... There is therefore no force to Purdue's argument that the

written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

Response to Arguments

6. The resposne asserts on page 14 of the remarks mailed 02/04/2009 that the examiner agreed the specification provides support for 60 to 500,000 probes. It is noted that the examiner did not agree that the specification has support for the range of 60 to 500,000 but that the specification does provide support for 338 spotted fragments (see pg. 8 lines 11-12), as well as 92, 90, 96, and 60 fragments (see pg. 32 lines 20-21), in addition to 500,000 probes (see pg. 11, lines 14-15), which did not indicate that the specification has support for the range and end point of 500,000.

New Grounds of Rejections

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-6, 8-14, and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gingeras et al. (US Patent 6228575) in view of Hayward et al. (Mol. Microbiology, 2000, 35(1), 6-14) as evidenced by DiResi (cited on 892 filed 11/19/2003).

With regard to claim 1 and 9, Gingeras et al. teach a method of oligonucleotide array for speculating and phenotyping organism by providing an array of known locations on a substrate comprising a plurality probes to reference DNA sequences hybridizing target nucleic acid sequence to array and based on hybridization pattern identifying the genotype of the first organisms (see column 3, lines 1-13 and column 4, lines 7-13). Gingeras et al. teach amplification of nucleic acid sample prior to hybridization (See column 8, lines 34-37) (providing amplified genomic sequences). Gingeras et al. teach hybridized nucleic acid are detected by detecting one or more labels attached to the sample nucleic acids and include fluorescein labels (see column 8, lines 46-57) (labeled DNA with a fluorescent dye). Gingeras et al. teach the screening method allows one to build up a data base of hybridization patterns corresponding to different species. Gingeras et al. teach identifying mycobacterium species by measuring fingerprint data (hybridization pattern on array) (see column 30, lines 65-67) by a collection of samples and based on these measurements a systematic way to predict species of each member of the collect by comparing the signal produced by the target at each hybridization site compared to the signal produced by Mt rpoB (see column 31, lines 1-5). Specifically, Gingeras et al. teach hybridization analysis of 7 mycobacteria species (reference samples) and teach that a reference sequence can be sequence of nucleotides, DNA (see column 12, lines 51-

53 and column 34, lines 45-51). Gingeras et al. teach fluorescently labeled amplicons from mycobacteria species hybridized to a DNA chip and comparing the hybridization pattern to amplicons hybridized to the DNA chip from M. tuberculosis (test bacteria) (see column 35, lines 15-25 and table 4). Gingeras et al. teach analyzing the fingerprint pattern of each species followed by classification analysis (calculating the hybridized DNA fluorescent dye signal and reference DNA fluorescence to determine identity) (See column 36, lines 35-51). Although Gingeras teach using known sequences of the rpoB gene, Gingeras teach that any gene sequence can be used (see column 9, lines 20-25). Furthermore, Gingeras teach that a tiling strategy using multiple probe sets (see column 10, lines 14-16) and teach arrays of all possible probes of a given length can be used (see column 16, lines 8-18). A tiling strategy of a microarray or an array of all possible probes of a given length will include random sequences.

With regard to claim 2-3 and 10-11, Gingeras et al. teach assaying biological samples, which refers to a sample obtained from an organism or clinical sample from a patient (See column 8, lines 22-34).

With regard to claim 4 and 12, Gingeras et al. teach assaying biological samples obtained from an organism (environmental sample) (see column 8, lines 22-25).

With regard to claim 6, 13, 14, and 26-27, Gingeras et al. teach hybridization patterns (producing hybridization profiles) correlated to species determination using mathematical pattern recognition algorithms (calculating by statistical analysis) (see column 30, lines 5-67 and column 31, lines 1-67).

With regard to claims 22-25, Gingeras teach array with a lower limit of 25, 50, or 100 probes to as many as 10^4, etc. probes (See column 16, lines 1-6)

Gingeras does not teach random amplified genomic sequences that are 1-2kb arrayed on a solid support nor teach unknown sequences.

Hayward et al. teach constructing a shotgun DNA microarray using random inserts from a genomic library and allows for analysis of genomes that have not been fully sequenced (see abstract). Hayward teach constructing a DNA microarray by printing 3648 PCR amplified inserts from a DNA library. Hayward et al. teach amplified inserts from 8000 independent clones were applied to the array and the average size was 1-2 kb (see pg. 7, array construction). Hayward teach labeling two different forms of Plasmodium with two different fluorescent labels to evaluate the differences among the two forms (see pg. 7, 2nd column, last paragraph). Hayward teach that fluorescence signals from Cy3 and Cy5 label were separately measured at each spot on the array and the red/green fluorescence ratio provided a measure of the relative abundance of the transcripts (see pg. 8, 1st column, 1st para). It is noted that Hayward teaches hybridized cDNA on glass arrays were processed and analyzed for fluorescence as previously described by DeRisi. DeRisi et al. reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio and normalization of the signal (claims 6, 14, 26 and 27) (see footnote 49 of DeRisi), accordingly it is an inherent property of the method of Hayward to include such a step.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining the species of an organism by providing a substrate comprising a plurality probes to reference DNA sequences as taught by Gingeras to include a shotgun DNA microarray of reference DNA sequences from multiple organisms as taught by Hayward that are 1-2kb in size to allow for a more robust analysis of

phenotyping organisms and to include detection of unsequenced genomes. The ordinary artisan would have been motivated to include a shotgun DNA microarray of reference bacterial strains in the method of Gingeras because Gingeras teach that other sequences can be detected in the method (see column 9 lines 20-25) and teach arrays of all possible probes of a given length can be used and therefore the method of Gingeras could be practiced using random amplified sequences from different organisms and furthermore Hayward teach that the microarray allows for analysis of genomes that have not yet been sequenced. Furthermore, because both Gingeras and Hayward teach analysis of genomic sequences of pathogenic organisms by DNA hybridization of microarrays, it would have been obvious to one of ordinary skill in the art to substitute one method, the construction of the shotgun microarray as taught by Hayward for the array of probes specific for rpoB gene as taught by Gingeras in order to achieve the predictable result of detecting bacterial species using DNA hybridization patterns using a DNA microarray.

10. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gingeras et al. (US Patent 6228575) in view of Hayward et al. (Mol. Microbiology, 2000, 35(1), 6-14) as evidenced by DiResi (cited on 892 filed 11/19/2003) and Legender (1998, cited on IDS).

With regard to claim 1 and 9, Gingeras et al. teach a method of oligonucleotide array for speculating and phenotyping organism by providing an array of known locations on a substrate comprising a plurality probes to reference DNA sequences hybridizing target nucleic acid sequence to array and based on hybridization pattern identifying the genotype of the first organisms (see column 3, lines 1-13 and column 4, lines 7-13). Gingeras et al. teach amplification of nucleic acid sample prior to hybridization (See column 8, lines 34-37) (providing amplified genomic sequences). Gingeras et al. teach hybridized nucleic acid are

detected by detecting one or more labels attached to the sample nucleic acids and include fluorescein labels (see column 8, lines 46-57) (labeled DNA with a fluorescent dye). Gingeras et al. teach the screening method allows one to build up a data base of hybridization patterns corresponding to different species. Gingeras et al. teach identifying mycobacterium species by measuring fingerprint data (hybridization pattern on array) (see column 30, lines 65-67) by a collection of samples and based on these measurements a systematic way to predict species of each member of the collect by comparing the signal produced by the target at each hybridization site compared to the signal produced by Mt rpoB (see column 31, lines 1-5). Specifically, Gingeras et al. teach hybridization analysis of 7 mycobacteria species (reference samples) and teach that a reference sequence can be sequence of nucleotides, DNA (see column 12, lines 51-53 and column 34, lines 45-51). Gingeras et al. teach fluorescently labeled amplicons from mycobacteria species hybridized to a DNA chip and comparing the hybridization pattern to amplicons hybridized to the DNA chip from M. tuberculosis (test bacteria) (see column 35, lines 15-25 and table 4). Gingeras et al. teach analyzing the fingerprint pattern of each species followed by classification analysis (calculating the hybridized DNA fluorescent dye signal and reference DNA fluorescence to determine identity) (See column 36, lines 35-51). Although Gingeras teach using known sequences of the rpoB gene, Gingeras teach that any gene sequence can be used (see column 9, lines 20-25). Furthermore, Gingeras teach that a tiling strategy using multiple probe sets (see column 10, lines 14-16) and teach arrays of all possible probes of a given length can be used (see column 16, lines 8-18). A tiling strategy of a microarray or an array of all possible probes of a given length will include random sequences. Gingeras does not

teach random amplified genomic sequences that are 1-2kb arrayed on a solid support nor teach determining an evenness value.

Hayward et al. teach constructing a shotgun DNA microarray using random inserts from a genomic library and allows for analysis of genomes that have not been fully sequenced (see abstract). Hayward teach constructing a DNA microarray by printing 3648 PCR amplified inserts from a DNA library. Hayward et al. teach amplified inserts from 8000 independent clones were applied to the array and the average size was 1-2 kb (see pg. 7, array construction). Hayward teach labeling two different forms of Plasmodium with two different fluorescent labels to evaluate the differences among the two forms (see pg. 7, 2nd column, last paragraph). Hayward teach that fluorescence signals from Cy3 and Cy5 label were separately measured at each spot on the array and the red/green fluorescence ratio provided a measure of the relative abundance of the transcripts (see pg. 8, 1st column, 1st para). It is noted that Hayward teaches hybridized cDNA on glass arrays were processed and analyzed for fluorescence as previously described by DeRisi. DeRisi et al. reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio and normalization of the signal (claims 6, 14, 26 and 27) (see footnote 49 of DeRisi), accordingly it is an inherent property of the method of Hayward to include such a step.

Legender teaches analysis of evenness to compare the diversity and shape of distribution to directly interpret species diversity (see pg. 243, 1st para). Legender teaches that evenness consists of comparing the measured diversity to the corresponding maximum value and teaches that interspecific competition is low the evenness value is high (see pg. 245, last para).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining the species of an organism by providing a substrate comprising a plurality probes to reference DNA sequences as taught by Gingeras to include a shotgun DNA microarray of reference DNA sequences from multiple organisms as taught by Hayward that are 1-2kb in size to allow for a more robust analysis of phenotyping organisms and to include detection of unsequenced genomes and include evenness value to determine species diversity as taught by Legender. The ordinary artisan would have been motivated to include a shotgun DNA microarray of reference bacterial strains in the method of Gingeras because Gingeras teach that other sequences can be detected in the method (see column 9 lines 20-25) and teach arrays of all possible probes of a given length can be used and therefore the method of Gingeras could be practiced using random amplified sequences from different organisms as well as include analysis of species diversity as taught by Legender and furthermore Hayward teach that the microarray allows for analysis of genomes that have not yet been sequenced. Furthermore, because both Gingeras and Hayward teach analysis of genomic sequences of pathogenic organisms by DNA hybridization of microarrays, it would have been obvious to one of ordinary skill in the art to substitute one method, the construction of the shotgun microarray as taught by Hayward for the array of probes specific for rpoB gene as taught by Gingeras in order to achieve the predictable result of detecting bacterial species using DNA hybridization patterns using a DNA microarray.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gingeras et al.

11. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ezaki et al. (Int. J. Sys. Bacteriol. 1989, vol. 39, pp. 224-229) in view of Hayward et al. (Mol. Microbiology,

2000, 35(1), 6-14) as evidenced by DiResi (cited on 892 filed 11/19/2003) and Legender (1998, cited on IDS).

Ezaki et al. teach a method of identifying bacteria by providing DNA-DNA hybridization from renaturation rates to determine genetic relatedness and thus identify bacterial species (see pg. 224, 1st column, 1st two para). Ezaki et al. teach DNA of bacterial strains were added to micro dilution plate (microchip, claim 5) (see pg. 224, 1st column, last para con't to 2nd column). Ezaki et al. teach hybridizing of DNA in micro dilution wells (see pg. 224, 2nd column, last para) followed by detection of hybridized DNA (see pg. 225, 1st column). Ezaki et al. teach analysis of at least four reference bacteria strain hybridization (reference strains, table 1). Ezaki et al. teach determining the presence of 70% homology (see figure 4) using fluorescently labeled reference DNA. Ezaki et al. teach identification without sequencing of pathogenic bacteria (see figure 4, 5, 8 and pg. 227, 1st column, last para). Ezaki et al. does not teach providing amplified random genomic sequences to create a plurality of arrayed elements, nor teach labeled target DNA with a first fluorescent dye and labeled reference DNA from a second fluorescent dye or determining an evenness value.

Hayward et al. teach constructing a shotgun DNA microarray using random inserts from a genomic library and allows for analysis of genomes that have not been fully sequenced (see abstract). Hayward teach constructing a DNA microarray by printing 3648 PCR inserts from a DNA library amplified (at least 96 arrayed elements, claims 22-25). Hayward et al. teach amplified inserts from 8000 independent clones were applied to the array and the average size was 1-2 kb (see pg. 7, array construction). Hayward teach labeling two different forms of Plasmodium with two different fluorescent labels to evaluate the differences among the two

forms (see pg. 7, 2nd column, last paragraph) (labeling with a first and second fluorescent dye). Hayward teach that fluorescence signals from Cy3 and Cy5 label were separately measured at each spot on the array and the red/green fluorescence ratio provided a measure of the relative abundance of the transcripts (see pg. 8, 1st column, 1st para) (calculating a ratio of fluorescent signal for target and reference at each element). It is noted that Hayward teaches hybridized cDNA on glass arrays were processed and analyzed for fluorescence as previously described by DeRisi. DeRisi et al. reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio and normalization of the signal (claims 6, 14, 26 and 27) (see footnote 49 of DeRisi), accordingly it is an inherent property of the method of Hayward to include such a step.

Legender teaches analysis of evenness to compare the diversity and shape of distribution to directly interpret species diversity (see pg. 243, 1st para). Legender teaches that evenness consists of comparing the measured diversity to the corresponding maximum value and teaches that interspecific competition is low the evenness value is high (see pg. 245, last para).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining the identification of a bacteria by DNA-DNA hybridization based upon homology using a micro dilution plate comprising a plurality of DNA from multiple organisms as taught by Ezaki to substitute the microdilution plate for a shotgun DNA microarray from multiple organisms and analysis of hybridization using fluorescently labeled test and reference DNA as taught by Hayward and include determining a high evenness value above 20 as taught by Legender to allow for a more robust analysis of phenotyping organisms without the need for sequencing the genome and an

analysis method that allows for a high throughput analysis of bacterial species identification. The ordinary artisan would have been motivated to substitute the micro dilution plate of Ezaki for the shotgun microarray taught by Hayward and thus include the method of constructing as well as the analysis of the shotgun DNA microarray as taught by Hayward in the method of Ezaki because neither Ezaki et al. nor Hayward require the knowledge of known genomic sequences and Hayward teach that the microarray allows for analysis of genomes that have not yet been sequenced and the shotgun microarray and analysis taught by Hayward allows for high throughput analysis with minimal amount of DNA as well as include analysis of an evenness value to determine species diversity as taught by Legendre. Furthermore, because both Ezaki and Hayward teach analysis of genomic sequences of pathogenic organisms by DNA hybridization of microarrays, it would have been obvious to one of ordinary skill in the art to substitute one method, the construction of the shotgun microarray as taught by Hayward for the DNA attachment to micro dilution plates as taught by Ezaki in order to achieve the predictable result of detecting bacterial species using DNA hybridization patterns using a shotgun DNA microarray.

Maintained Rejections

Claim Rejections - 35 USC § 103

12. Claims 1, 3, 5-6, 8-9, 11, 13-14, and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ezaki et al. (Int. J. Sys. Bacteriol. 1989, vol. 39, pp. 224-229) in view of Hayward et al. (Mol. Microbiology, 2000, 35(1), 6-14) as evidenced by DiResi (cited on 892

filed 11/19/2003). This rejection was previously presented and has been rewritten to address the amendment to the claims.

Ezaki et al. teach a method of identifying bacteria by providing DNA-DNA hybridization from renaturation rates to determine genetic relatedness and thus identify bacterial species (see pg. 224, 1st column, 1st two para). Ezaki et al. teach DNA of bacterial strains were added to micro dilution plate (microchip, claim 5) (see pg. 224, 1st column, last para con't to 2nd column). Ezaki et al. teach hybridizing of DNA in micro dilution wells (see pg. 224, 2nd column, last para) followed by detection of hybridized DNA (see pg. 225, 1st column). Ezaki et al. teach analysis of at least four reference bacteria strain hybridization (reference strains, table 1). Ezaki et al. teach determining the presence of 70% homology (see figure 4) using fluorescently labeled reference DNA. Ezaki et al. teach identification without sequencing of pathogenic bacteria (see figure 4, 5, 8 and pg. 227, 1st column, last para). Ezaki et al. does not teach providing amplified random genomic sequences to create a plurality of arrayed elements, nor teach labeled target DNA with a first fluorescent dye and labeled reference DNA from a second fluorescent dye.

Hayward et al. teach constructing a shotgun DNA microarray using random inserts from a genomic library and allows for analysis of genomes that have not been fully sequenced (see abstract). Hayward teach constructing a DNA microarray by printing 3648 PCR inserts from a DNA library amplified (at least 96 arrayed elements, claims 22-25). Hayward et al. teach amplified inserts from 8000 independent clones were applied to the array and the average size was 1-2 kb (see pg. 7, array construction). Hayward teach labeling two different forms of Plasmodium with two different fluorescent labels to evaluate the differences among the two forms (see pg. 7, 2nd column, last paragraph) (labeling with a first and second fluorescent dye).

Hayward teach that fluorescence signals from Cy3 and Cy5 label were separately measured at each spot on the array and the red/green fluorescence ratio provided a measure of the relative abundance of the transcripts (see pg. 8, 1st column, 1st para) (calculating a ratio of fluorescent signal for target and reference at each element). It is noted that Hayward teaches hybridized cDNA on glass arrays were processed and analyzed for fluorescence as previously described by DeRisi. DeRisi et al. reference discloses that processing and recording of signals comprises calculation of a hybridization signal intensity ratio and normalization of the signal (claims 6, 14, 26 and 27) (see footnote 49 of DeRisi), accordingly it is an inherent property of the method of Hayward to include such a step.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining the identification of a bacteria by DNA-DNA hybridization based upon homology using a micro dilution plate comprising a plurality of DNA from multiple organisms as taught by Ezaki to include a shotgun DNA microarray from multiple organisms and analysis of hybridization using fluorescently labeled test and reference DNA as taught by Hayward to allow for a more robust analysis of phenotyping organisms without the need for sequencing the genome and an analysis method that allows for a high throughput analysis of bacterial species identification. The ordinary artisan would have been motivated to substitute the micro dilution plate of Ezaki for the shotgun microarray taught by Hayward and thus include the method of constructing as well as the analysis of the shotgun DNA microarray as taught by Hayward in the method of Ezaki because neither Ezaki et al. nor Hayward require the knowledge of known genomic sequences and Hayward teach that the microarray allows for analysis of genomes that have not yet been

sequenced and the shotgun microarray and analysis taught by Hayward allows for high throughput analysis with minimal amount of DNA. Furthermore, because both Ezaki and Hayward teach analysis of genomic sequences of pathogenic organisms by DNA hybridization of microarrays, it would have been obvious to one of ordinary skill in the art to substitute one method, the construction of the shotgun microarray as taught by Hayward for the DNA attachment to micro dilution plates as taught by Ezaki in order to achieve the predictable result of detecting bacterial species using DNA hybridization patterns using a shotgun DNA microarray.

13. Claims 2, 4 and 10, 12 rejected under 35 U.S.C. 103(a) as being unpatentable over Ezaki et al. (Int. J. Sys. Bacteriol. 1989, vol. 39, pp. 224-229) in view of Hayward et al. (Mol. Microbiology, 2000, 35(1), 6-14) as evidenced by DiResi (cited on 892 filed 11/19/2003).as applied to claim 1, 3, 5-6, 8-9, 11, 13-14, and 22-27 above, and further in view of Gingeras (US Patent 6228575).

The method of Ezaki in view of Hayward as evidence by DiResi is set forth in section 10 above. Ezaki in view of Hayward as evidence by DiResis does not teach the test sample is from a sample from a subject or environmental isolate.

Gingeras et al. teach a method of oligonucleotide array for speculating and phenotyping organism by providing an array of known locations on a substrate comprising a plurality probes to reference DNA sequences hybridizing target nucleic acid sequence to array and based on hybridization pattern identifying the genotype of the first organisms(see column 3, lines 1-13 and column 4, lines 7-13). Gingeras et al. teach assaying biological samples, which refers to a sample obtained from an organism or clinical sample from a patient (See column 8, lines 22-34)

(claims 2 and 10). Gingeras et al. teach assaying biological samples obtained from an organism (environmental sample) (see column 8, lines 22-25) (claims 4 and 12).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of determining the species of an organism by providing a substrate comprising a plurality probes to reference DNA sequences as taught by Ezaki in view of Hayward as evidence by Desiri to include test bacteria that is pathogenic and obtained from samples from a subject as well as environmental isolated, as taught by Gingeras, to improve the method of identification of bacteria species as taught by Ezaki in view of Hayward as evidence by Desiri. The ordinary artisan would have been motivated to improve the method of identifying bacteria to include test bacteria obtained from subjects, environmental isolates, as well as test bacteria that was pathogenic because Gingeras teach a method of bacteria identification that includes pathogenic bacteria obtained from subjects and environmental isolated. Furthermore, because both Ezaki, Hayward, and Gingeras teach analysis of genomic sequences of pathogenic organisms by DNA hybridization of microarrays, it would have been obvious to one of ordinary skill in the art to substitute the type of test bacteria being analyzed, bacteria from a subject or environmental isolated as taught by Gingeras for the bacteria tested in Ezaki in view of Hayward as evidence by Desiri in order to achieve the predictable result of detecting bacterial species using DNA hybridization patterns using a DNA microarray.

Response to Arguments

14. The response traverses the rejections on pages 9-13 of the remarks mailed 02/04/2009.

15. It is noted that the rejections presented in section 10 and 11 are new grounds of rejection however applicants remarks with regard to Hayward et al. may also pertain to the rejections above. Applicants assert that there is no basis for combination and that Hayward is non-

analogous art as Hayway is directed to studying gene expression and not identifying bacterial species and gene expression is not within the field of speciation. This response has been thoroughly reviewed but not found persuasive. It is noted that Hayward was not cited to teach gene expression but to teach construction of a microarray that allows for analysis of unknown sequences. Furthermore, Hayward is within the field of the claimed invention was both the claimed invention and Hayward require nucleic acid hybridization on a solid support for identification, thus Hayward is within the field of the claimed invention.

16. The response asserts that Ezaki teaches whole genome hybridization and there is nothing in Ezaki that would motivate one skilled in the art to depart from whole genome hybridization. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, determination of obviousness is on what a person of ordinary skill in the pertinent art would have known at the time of the invention and on what a person would have reasonably expected to have been able to do in view of that knowledge. Thus, a person of ordinarily skill in the art based on the teaching of Hayward on construction microarray for the analysis of sequences that are known would have expected to be able to adapt this microarray with the method of Ezaki to identify bacteria species of which their genomes have not yet been sequenced. Additionally, in response to applicant's arguments against the references

individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response asks how the combination of Ezaki and Hayward would work. The response asserts that Hayward uses techniques on genomes that have not yet been sequences and uses this on a single genome and does not make arrays of multiple genomes let alone teach a method of sorting out the potentially overwhelming confusion when multiple genomes are arrayed with random sequences. This response has been thoroughly reviewed but not found persuasive. The examiner has addressed that the construction of the microarray of Hayward would be used in the method of Ezaki, thus the teachings of Ezaki and analysis of multiple genomes as taught by Ezaki would encompass replacement of the solid support of Ezaki for the microarray of Hayward. If applicant is asserting that the use of an array with random sequences arrayed from multiple genomes would not work, then it is unclear how applicants invention would work as the combination of Ezaki and Hayward would render the invention obvious. In response to applicants request that the Examiner provide and demonstrate that the combination would work, the Office does not have the facilities for examining and comparing the applicant's methods with the combined methods of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed invention and that of the prior art.

The response asserts that the combination is improper and all of the elements are not taught. The response asserts that the combination does not teach random sequences and Hayward is not random, does not teach a mere fraction of the genome, nor teach labeled target and reference DNAs. This response has been thoroughly reviewed but not found persuasive.

The combination of Ezaki and Hayward does teach random generation of amplified products as mung bean nuclease is not specific for a specific nucleic acid sequence thus the fragments that are generated by Hayward do not have any definite sequence and thus are random. The claims do not require that a mere fraction of the genome is used as the sample, the claims require that it permits a sampling of 1-3% of the genome, which does not limit the claim to only 1-3% of genome but encompasses sample of *at least* 1-3% of the genome as the claims are drawn to a process comprising providing a solid support so as to permit the sampling of 1-3% of the genome, thus the claims merely require that the support is able to perform this function and thus analysis of the entire genome would encompass analysis of 1-3%. Additionally, Ezaki and Hayward do teach labeled reference and target DNA as Hayward teaches fluorescence label of both samples.

17. With regard to applicants traversal of Gingeras teaching known sequences, it is noted that Gingeras was not added to the reference nor applied to the rejection as teaching known sequences. Gingeras was merely cited to teach the sample can be from a subject or environmental isolate.

Conclusion

18. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAE BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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